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(58) Field of search
A5B

(54) Effervescent tablets

(57) Effervescent tablet formations which permit higher oral dosages of certain drugs, such as Fenbufen, to be administered with better patient compliance with the dosage regimen comprise a pharmaceutically acceptable weak acid e.g. citric or tartaric acid and a pharmaceutically acceptable carbonate e.g. sodium carbonate.

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SPECIFICATION

Pharmaceutical Tablet Preparations

This invention relates to unit dosage forms of non-steroidal anti-inflammatory drugs which permit the administration of high dosages of the active component.

In recent years a number of non-steroidal anti-inflammatory therapeutic agents have become available for the treatment of conditions such as mild rheumatoid arthritis, osteoarthritis, minor rheumatic conditions, sprains, strains and sports injuries. The main advantage of these therapeutic agents is that, in general, they cause few and relatively mild side effects whilst in many cases being similar in efficacy to aspirin or even indomethacin and phenylbutazone.

However, in some cases relative high dosages of the therapeutic agent are required for best clinical effect. For example, the normally recommended dose of Fenbufen (γ-oxo-(1,1'-biphenyl)-4-butanoic acid) for the treatment of arthritic conditions is 300 mg in the morning and 600 mg in the evening, taken orally, and there are indications that a better response may be obtained if the morning dose is increased to 600 mg.

It is well known that, in order to enhance patient compliance with the prescribed dosage regimen of any given therapeutic agent, it is desirable that the dosage to be taken at any one time should be presented in unit dosage form, be it a single tablet, capsule, etc. The ability to provide unit dosage forms containing all the therapeutic agent to be administered at any one time is particularly important for elderly patients. It will be appreciated that many of the conditions for which non-steroidal anti-inflammatory agents such as Fenbufen are prescribed are those to which such patients are especially prone.

Oral formulations containing high dosages, for example 600 mg, of Fenbufen and some other non-steroidal anti-inflammatory therapeutic agents present particular difficulty. A conventional tablet containing 600 mg of Fenbufen may be up to 2 or more centimetres in diameter, which is far too large to ensure satisfactory patient compliance. Attempts have therefore been made to formulate the Fenbufen as a syrup, but the resulting preparations have not been satisfactory since they have not adequately masked the extremely unpleasant taste of Fenbufen, and so hinder rather than assist the prospects for patient compliance.

It has now been found, in accordance with the present invention, that these problems of satisfactorily formulating oral unit dosage forms with high dosages of, for example, Fenbufen, can at least substantially be overcome by presenting the active therapeutic agent as an effervescent tablet which is formulated from ingredients having the effect of reducing the pH (i.e. increasing the acidity) when the tablet is placed in water. The solubility of eg Fenbufen in water decreases with decreasing pH of the aqueous system. Consequently, when the effervescent tablet of the present invention is placed in water, most of the active ingredient goes into suspension, rather than into solution, as the tablet disintegrates, and in suspension form its unpleasant taste is significantly less noticeable than in solution. If the tablet contains a large dosage of Fenbufen, then it will still be of large size, but this fact will not hinder patient compliance since the tablet as such is not take by the patient.

In the preferred embodiments of the invention, the tablet is formulated from effervescent-producing excipients which act by generating carbon dioxide when the tablet is placed in water. The carbon dioxide thus causes not only the required effervescence but also serves to achieve the desired solubility-decreasing increase in acidity. Suitable excipients for this purpose are weak acids such as citric and tartaric acids together with a carbonate, more especially sodium bicarbonate, although other carbonate sources such as sodium glycine carbonate are effective. The quantities of these carbon dioxide-evolving excipients should preferably be such that the pH of the water is reduced to about pH 4.0 to 6.5, preferably to about pH 5.5 to 6.0, at which level Fenbufen, for example, is only about 0.002% soluble. Typically, therefore, the tablet will contain from 18 to 32 percent by weight, preferably from 23 to 27 percent by weight, of weak acid, and from 25 to 30 percent by weight of the carbonate source.

It is especially preferred to use as the carbonate source sodium bicarbonate which has been treated to drive off water, so that there is present about 10% by weight of sodium carbonate. This minor content of sodium carbonate is then available to react with any atmospheric moisture into which the tablet comes into contact, and thus helps to maintain the stability of the tablet.

The tablet may also contain other conventional excipients, in conventional quantities. In particular, the tablet will generally contain a disintegrating agent, such as Explotab (sodium starch glycolate) or Ac-di-sol (croscarmellose sodium Type A), to help break down into a fine suspension the relatively large particles which are formed by the effervescence, sa well as a lubricant such as magnesium stearate or DK ester 20W, a binder such as polyvinyl pyrrolidone to aid granulation and a compressible sugar such as sorbitol or mannitol to aid compression during the tabletting operation. A sweetening agent such as saccharin may be incorporated in order to enhance further the palatability of the tablet.

The effervescent tablet of this invention can be produced by conventional tabletting procedures well known to those skilled in the art. Once manufactured, the tablet should be stored out of contact with atmospheric moisture, and preferably is vacuum foil wrapped.

Examples of preferred effervescent tablet formulations in accordancce with the present inv ntion will now be given. In each case the active ingredient is Fenbufen, but those skilled in the art will recognize that the present teachings will be applicable to other non-steroidal anti-inflammatory therapeutic agents.

EXAMPLE 1

An efferv scent 450 mg. Fenbufen tablet is formed of the following composition:.

Ingredients	Parts by weight (mg.)	
Fenbufen powder	450	Part 1
Croscarmellose sodium type A	90	
Saccharin sodium	20	
Polyvinylpyrrolidone	30	
Citric acid anhydrous	801.3	Part 2
Sodium bicarbonate dried	912.7	
Sorbitol powder	600	
Flavours	170	
Magnesium stearate	13	
DK ester 20W	13	

The polyvinylpyrrolidone (PVP) is dissolved in industrial methylated spirit 740P (IMS) to give an approximately 30% solution. The remaining ingredients of Part 1 are mixed together and granulated with the PVP solution. The granulation is tray dried until the moisture is below 1%. The Part 2 ingredients are mixed together and granulated with IMS. The granulation is dried as before. Both granulations are transferred to an area maintained at below 40% RH and milled. The appropriate quantities of granulations 1 and 2 are mixed with the remaining ingredients and compressed into 3.1 gram tablets.

When one tablet is added to approximately 100 ml. water, it disperses with effervescence to give, within approximately 2 minutes, a flavoured suspension which largely masks the burning taste of Fenbufen.

EXAMPLE 2

An efferverscent 600 mg. Fenbufen tablet is formed of the following composition in the manner described in Example One above:

Ingredients	Parts by weight(mg.)	
Fenbufen powder	600	Part 1
Croscarmellose sodium type A	120	
Saccharin sodium	26.7	
Polyvinylpyrrolidone	40	
Citric acid anhydrous	801.3	Part 2
Sodium bicarbonate dried	912.7	
Sorbitol powder	600	
Flavours	170	
Magnesium stearate	13	
DK ester 20W	13	

The composition is compressed into 3.3 gram tablets which, like the tablets of Example 1, possess enhanced palatability.

CLAIMS

1. An oral unit dosage form of a therapeutically active compound which is substantially insoluble in water at acid pH, said unit dosage form being a tablet which comprises, in addition to the therapeutically active compound, one or more ingredients which, when the tablet is placed in water, cause the tablet to effervesce and the pH of the water to be lowered, whereby the therapeutically active compound substantially goes into suspension.

2. A tablet according to Claim 1, wherein said therapeutically active compound is Fenbufen.

3. A tablet according to Claim 2, containing 600 mg of Fenbufen.

4. A tablet according to any preceding Claim, wherein said one or ingredients react to generate carbon dioxide wh n the tablet is placed in water.

5. A tablet according t Claim 4, wherein said carbon dioxide-generating ingredients comprise a pharmac utically acceptable weak acid and a pharmaceutically acceptable carbonate.

6. A tablet according to Claim 5, wherein said weak acid is selected fr m citric acid and tartaric acid, and said carbonate is sodium bicarbonate.

7. A tablet according to Claim 5 or Claim 6, wherein said weak acid and said carbonate are present in

amounts such that, when the tablet is placed in water, the pH thereof is reduced to within the range pH 4.0—6.5.

8. A tablet according to Claim 7, wherein said pH range is pH 5.5—6.0.

9. A tablet for oral administration of Fenbufen, substantially as described in either of the Examples herein.

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